Complete Summary

GUIDELINE TITLE

Dyspepsia.

BIBLIOGRAPHIC SOURCE(S)

Institute For Clinical Systems Improvement (ICSI). Dyspepsia. Bloomington (MN): Institute For Clinical Systems Improvement (ICSI); 2003 Jan. 48 p.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Dyspepsia, including gastric ulcer dyspepsia; duodenal ulcer dyspepsia; or non-ulcer (functional) dyspepsia
- Gastroesophageal reflux disease (GERD)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology

Internal Medicine
Radiology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To increase the use of recommended methods for evaluating dyspepsia
- To increase appropriate pharmaceutical treatment of patients with dyspepsia
- To decrease complications associated with peptic ulcer disease
- To improve (functional) outcomes and satisfaction of patients with dyspepsia

TARGET POPULATION

Adult males and non-pregnant adult females with symptoms of epigastric pain or discomfort on greater than 25% of days over the past 4 weeks. Individuals with nausea, heartburn or acid regurgitation are eligible.

This guideline does not stipulate the exact symptoms that define dyspepsia, thus allowing the clinician some latitude in identifying the patients to whom this guideline can be applied.

This guideline does not apply to patients whose symptoms are characteristic of biliary tract disease, pancreatic disease or irritable bowel syndrome.

INTERVENTIONS AND PRACTICES CONSIDERED

Dyspepsia

Diagnostic Assessment

1. Medical history including history of prior documented ulcer
2. Evaluate symptoms, with particular attention to presence of alarm features
3. Endoscopy
4. Multiphase upper gastrointestinal (UGI) studies
5. Helicobacter pylori (H. pylori) serology or urea breath testing (UBT)
6. Fasting serum gastrin (to rule out Zollinger-Ellison in patients who do not use nonsteroidal anti-inflammatory drugs [NSAIDs])
7. Biopsy for H. pylori

Treatment

1. Eradicative therapy for H. pylori

- Proton pump inhibitor (PPI) drugs, such as omeprazole (Prilosec®), lansoprazole (Prevacid®), rabeprazole (AcipHex®), pantoprazole (Protonix®), or esomeprazole (Nexium®)
- Clarithromycin
- Amoxicillin
- Tetracycline
- Metronidazole
- Bismuth

2. Histamine-2 receptor agonists (H_2RA)
    - cimetidine (Tagamet® or generics)
    - ranitidine (Zantac® or generics)
    - famotidine (Pepcid®)
    - nizatidine (Axid®)
3. Discontinuation of nonsteroidal anti-inflammatory drugs
4. Smoking cessation

Gastroesophageal Reflux Disease (GERD)

Diagnostic Assessment

1. Flexible esophagogastroduodenoscopy
2. 24-hour pH monitoring

Treatment

1. Behavioral/lifestyle modifications
    - Dietary changes (avoid caffeine, chocolate, fats, alcohol, decaffeinated tea and coffee, caffeinated soft drinks, citrus juices, peppermint, and spearmint)
    - Weight loss
    - Avoiding large meals
    - Body positioning (avoid lying down after eating, elevating head of bed)
    - Tobacco cessation
2. Changing medications that can lower the lower esophageal sphincter (LES), such as theophylline, calcium channel blockers, and barbiturates
3. Use of antacids and over-the-counter histamine-2 receptor agonists
4. Full-dose H_2RA therapy (cimetidine, ranitidine, famotidine, and nizatidine)
5. Step-down therapy
6. Proton pump inhibitors for patients with erosive esophagitis or worse

MAJOR OUTCOMES CONSIDERED

- Efficacy of Helicobacter pylori testing (positive or negative)
- Sensitivity, specificity, positive and negative predictive value of diagnostic instruments
- Efficacy/side effects of medications
- Recurrence of peptic ulcer disease
- Recurrence of esophagitis
- Incidence of gastric cancer
- Patient symptoms
- Healing rates
- Costs of diagnostic tests and treatments

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong or exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

   Class A:

   - Randomized, controlled trial

   Class B:

   - Cohort study

   Class C:

   - Non-randomized trial with concurrent or historical controls
   - Case-control study
   - Study of sensitivity and specificity of a diagnostic test
   - Population-based descriptive study

   Class D:

   - Cross-sectional study
   - Case series
   - Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

   Class M:

   - Meta-analysis
   - Systematic review

- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developer reviewed published cost analyses.

Helicobacter pylori testing appears to be a cost-effective approach for long-term dyspepsia management. (See Discussion Appendix C in the original guideline document.) A decision-analytic model shows that an approach utilizing a combination of empiric therapy for Helicobacter pylori and antisecretory therapy was superior to antisecretory therapy alone. In addition, initial therapy for Helicobacter pylori guided by serological testing was the most cost-effective option if the cost of the serologic test was $12 or less. When endoscopy can be provided for less than $500 including all fees, immediate endoscopy is more cost-effective.

A second decision analysis comparing the costs and outcomes of initial anti-Helicobacter pylori treatment to initial endoscopy among those who are Helicobacter pylori antibody positive shows initial therapy as the most cost-effective management strategy.

Additional cost-benefit analyses have been performed. Refer to the original guideline document for all citations.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary and a written response is prepared to address each of the responses received from member groups. Two members of the Committee on Evidence-Based Practice carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer and other practice systems. Evaluation and assessment occurs throughout the pilot test phase, which usually lasts for three-six months. At the end of the pilot test

phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, the Committee on Evidence-Based Practice reviews the revised guideline and approves it for release.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

The recommendations for the management of dyspepsia are presented in the form of a primary algorithm, Dyspepsia, with 19 components, and a secondary algorithm, Gastroesophageal Reflux Disease (GERD), with an additional 12 components (for a total of 31 components), accompanied by detailed annotations. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III and Not Assignable) definitions are repeated at the end of the Major Recommendations field.

Clinical Highlights

1. Send patients with dyspepsia plus one of the following alarm features for urgent endoscopic evaluation. Suggested time frames for the urgency of endoscopy are provided with each of the alarm features listed. (Annotations #2, 3)
    - Melena (within 1 day)
    - Hematemesis (within 1 day)
    - Persistent vomiting (7-10 days)
    - Anemia (7-10 days)
    - Acute onset dysphagia (within 1 day)
    - Weight loss greater than 5% (involuntary) (7-10 days)
2. Patients 50 years of age and older with symptoms of uncomplicated dyspepsia should be evaluated with non-urgent upper endoscopy. (Annotation #9)
3. Patients with dyspepsia and prior documentation of ulcer, but no alarm features or reflux symptoms, should receive Helicobacter pylori (H. pylori) testing and if positive, eradicative therapy. (Annotations #4, 5, 10, 11)
4. Patients with gastroesophageal reflux should receive step-up therapy. (Annotations #6, 20, 23, 25, 27-31)
5. Patients with dyspepsia and negative testing results for H. pylori should be treated empirically with histamine-2 receptor agonists (H_2RA). (Annotation #12)

Dyspepsia Algorithm Annotations

1. Dyspepsia

   Dyspepsia is defined as pain or discomfort felt to arise in the upper gastrointestinal (GI) tract with symptoms on greater than 25% of days over the past 4 weeks. Patients with epigastric pain or discomfort, nausea, heartburn or acid regurgitation are eligible. This guideline does not apply to patients whose symptoms are characteristic of biliary tract disease, pancreatic disease or irritable bowel syndrome.

2. Are There Alarm Features?

   Alarm features should be sought in all patients presenting with dyspepsia. If alarm features are present, endoscopy should be performed (suggested time frames for urgency of endoscopy are provided with each of the alarm features listed). Alarm features is a term that is used frequently in the dyspepsia literature to describe clinical features that may suggest underlying disease that should be diagnosed and treated without the delay of an empiric therapeutic trial. Alarm features frequently cited are:

   - Anemia (7-10 days)
   - Acute onset dysphagia (within 1 day)
   - Hematemesis (within 1 day)
   - Melena (within 1 day)
   - Persistent vomiting (7-10 days)
   - Weight loss >5% (involuntary) (7-10 days)

   Evidence supporting this recommendation is of class: D

3. Endoscopy for Alarm Features/Out of Guideline

   Endoscopy is the procedure of choice for evaluation of dyspepsia. A single contrast barium study is not an acceptable alternative. Multiphase upper gastrointestinal (UGI) studies performed by radiologists with specific training in gastrointestinal radiology are an acceptable alternative to endoscopy.

   If specialty radiologic expertise with multiphase barium UGI is available, UGI study should be viewed as an alternative to endoscopy. Otherwise, endoscopy provides greater sensitivity for the diagnosis of peptic ulcer disease. [Conclusion Grade III: See Discussion Appendix A of the original guideline document, Conclusion Grading Worksheet - Annotation #3.]

4. Prior Documented Ulcer?

   In patients presenting with dyspepsia and a prior documented ulcer, referral to a gastroenterologist is appropriate. Documentation of the prior ulcer must include an endoscopy or barium UGI report confirming the presence of an ulcer.

5. H. pylori Testing, Eradication/Case Management

Case management should begin with H. pylori serology. Those who are positive should receive eradicative therapy. (Refer to Main Algorithm Annotation #10).

Patients who are serology negative should receive a full therapeutic dose of H_2RA. Consider discontinuing nonsteroidal anti-inflammatory drug (NSAID) and/or smoking. Two months of treatment should be provided to responders.

Symptoms continuing for a month or more into treatment should prompt endoscopy regardless of initial treatment. Further evaluation may be necessary.

Maintenance H_2RA treatment is not indicated for those experiencing symptom resolution after treatment. Patients with complicated peptic ulcer disease may be considered for maintenance treatment using H_2RA at one-half the therapeutic dose after successful treatment. Documenting H. pylori eradication should be limited to those with a history of complicated peptic ulcer disease.

6. The Single Dominant Symptom is Heartburn or Acid Regurgitation?

The patient has heartburn (retrosternal pain) or acid regurgitation (a sour or bitter taste in mouth) as the single dominant symptom. These symptoms are sought because their presence is associated with a probability of 89% and 95%, respectively, of gastroesophageal reflux disease (GERD) based on studies using esophageal pH monitoring as the reference standard. The goal is to minimize the number of patients with ulcer referred to the GERD algorithm.

Evidence supporting this recommendation is of class: C

9. Is Patient Age 50 or Older, or at Increased Risk of Gastric Cancer?

Esophagogastroduodenoscopy, performed within 4-8 weeks, may be appropriate in patients over the age of 50 because the incidence of gastric cancer is increased, but no study to date has shown improved outcomes. [Conclusion Grade II: See Discussion Appendix B of the original guideline document, Conclusion Grading Worksheet - Annotation #9.]

10. Is H. pylori Qualitative Serology Positive?

An approach to possible gastric or duodenal ulcer disease should include a strategy to eliminate Helicobacter pylori. Sensitive and specific point-of-care testing is commercially available and can provide 5-10 minute turnaround using whole blood, serum or plasma. Helicobacter pylori urea breath testing (UBT) has similar sensitivity and superior specificity. If the cost and availability of urea breath testing is similar to serology in the local practice environment, it would be the preferred test.

Helicobacter pylori testing appears to be a cost-effective approach for long-term dyspepsia management. [Conclusion Grade II: See Discussion

Appendix C of the original guideline document, Conclusion Grading Worksheet - Annotation #10.]

11. Treatment for H. pylori

There are six regimens Food and Drug Administration (FDA) approved for treatment of Helicobacter. In addition, many more are published in the literature. The two following therapies are equally effective in eradicating H. pylori (95% effective) and in preventing gastrointestinal ulcer recurrence (80% effective). These two therapies represent a combination of ease of compliance and cost. Patient compliance is very important. The patient can take all drugs simultaneously. The choice of regimen may be influenced by frequency of dosing or patient tolerance or highly variable local acquisition costs.

Regardless of which therapy course is chosen, patients with significant symptoms at presentation may continue to use a standard dose of a proton pump inhibitor (PPI) or H_2RA for 3 extra weeks at the end of the combination drug treatment.

Treatment choice #1: 7-day treatment

- PPI standard dose twice daily x 7 days
- Clarithromycin: 500 mg twice daily x 7 days**
- Amoxicillin: 1 gram twice daily x 7 days*

Treatment choice #2: 7-day treatment

- PPI standard dose twice daily x 7 days
- Tetracycline: 250 mg four times daily (qid) x 7 days*
- Metronidazole: 500 mg twice daily x 7 days**
- Bismuth: chew 2 tablets four times daily x 7 days

* Substitute metronidazole 500 mg twice daily x 7 days if patient is intolerant to tetracycline or amoxicillin.

** Substitute amoxicillin 1 gram twice daily x 7 days if suspect H. pylori resistance to metronidazole.

Proton Pump Inhibitors (PPI)—Generic Names (Trade Names) and Usual Adult Dose

- Omeprazole (Prilosec®) -- 20 mg every day (qd)
- Lansoprazole (Prevacid®) -- 30 mg qd
- Rabeprazole (AcipHex®) -- 20 mg qd
- Pantoprazole (Protonix®) -- 40 mg qd
- Esomeprazole (Nexium®) -- 40 mg qd

12. Empiric Trial of Full Dose H_2RA/Address Nonsteroidal Anti-Inflammatory Drug (NSAID) Use

Empiric Trial

The four available histamine-2 receptor antagonists (H_2RA) appear to be equivalent in efficacy and in adverse event profiles in the management of acid-peptic disorders when given in equipotent acid-suppressive doses. Full-dose therapy for four weeks as an empiric trial is recommended.

Histamine-2 Receptor Antagonists (H_2RA) – Generic Names (Trade Names) and Usual Adult Dose

- Cimetidine (Tagamet® and generics) -- 400 mg twice daily (bid) or 800 mg at bedtime (hs)
- Ranitidine (Zantac® and generics) -- 150 mg bid or 300 mg hs
- Famotidine (Pepcid®) -- 20 mg bid or 40 mg hs
- Nizatidine (Axid®) -- 150 mg bid or 300 mg hs

Patients on nonsteroidal anti-inflammatory drugs (NSAIDs)

Patients on NSAIDs should have these discontinued if possible. If it is not possible to discontinue NSAIDs, a duration of therapy of 12 weeks is recommended. This recommendation is based on well documented higher healing rates in patients with gastric as well as duodenal ulcers treated for a duration of twelve weeks compared to eight weeks. (See also Main Algorithm Discussion and References #15 in the original guideline document).

13. Symptoms Persist >4 Weeks?

Although ulcer healing may take 8 weeks or more, the majority of patients with gastric or duodenal ulcer have improvement in symptoms at 4 weeks.

14. Endoscopy Positive?

Endoscopy is the procedure of choice in most situations for evaluation of dyspepsia. If an ulcer is seen, a biopsy for H. pylori should be taken. A single contrast barium study is not an acceptable alternative. Multiphasic UGI studies performed by radiologists with specific training in gastrointestinal radiology are an acceptable alternative to endoscopy.

15. Case Management

Patients with an ulcer should have an H. pylori breath test if their stomach was not biopsied at the time of endoscopy. Treatment to eradicate H. pylori should be provided to those infected. If previously treated for H. pylori, a different regimen should be used and provided for 14 days, not 7. Metronidazole should be substituted for amoxicillin in the patient who has received amoxicillin previously. By either diagnostic route, if not infected with H. pylori, review NSAID use and smoking history as appropriate. Those who do not use NSAIDs should have Zollinger-Ellison excluded with a fasting serum gastrin.

16. Continue Treatment for 8 Weeks Total Course and Then Stop

Data on healing rates in both gastric and duodenal ulcers suggest that treatment with antiulcer agents should be continued to complete a course of eight weeks. The most effective agents for the majority of patients are H_2RAs. Patients who continue NSAIDs during treatment for peptic ulcers, particularly gastric ulcers, should have the duration of H_2RA treatment extended to twelve weeks total.

17. Non-Ulcer Dyspepsia

Most patients who undergo endoscopy for dyspepsia will not have a positive finding to explain the symptoms. The terms "non-ulcer" or "functional dyspepsia" have been used to label this situation. No medical treatment is clearly of proven benefit. On a case-by-case basis, elimination of certain foods (e.g., caffeine, alcohol, fat, etc.) or medications (e.g., NSAIDs) may help. On a similar individual basis, eradication of Helicobacter pylori (if not already done), treatment with a PPI, prokinetic or low-dose tricyclic antidepressant, and exploration of the contribution of psychologic distress may prove beneficial. Additional testing may be necessary, but overtesting, overtreatment, and over-referral should be avoided. Short-term empiric trials could be considered.

Gastroesophageal Reflux Disease (GERD) Algorithm Annotations

20. Phase I (4 week trial) Behavioral Modification and Over-the-Counter (OTC) H_2RA/Antacids

If these modifications have already been tried by the patient, then advancement to Phase II treatment would be appropriate.

Initial treatment of GERD should consist of a four-week, or longer, trial of more long-term behavioral modifications designed to help reduce reflux both structurally, promoting proper function of the lower esophageal sphincter (LES), and also reducing acidity of gastric juices. This treatment consists of the following:

1. Dietary changes
    A. Avoid caffeine, chocolate, fats, alcohol, and decaffeinated tea and coffee, caffeinated soft drinks, citrus juices, peppermint, and spearmint
    B. Weight loss if indicated
    C. Avoid large meals that may increase intra-abdominal pressure
2. Avoid lying down after eating for 2-3 hours as well as elevating the head of the bed by 6-8 inches.
3. Avoid use of tobacco, with promotion of tobacco and nicotine cessation. Also consider changing medications that can lower the lower esophageal sphincter pressure, i.e., Theophylline, calcium channel blockers, and barbiturates.
4. Use of antacids on an as needed basis as well as the use of over-the-counter H_2RA may be of benefit.

The time frame of four weeks was selected for implementation of these behavioral modifications. These modifications may also take longer than four

weeks to implement for the best effect, i.e., weight loss and tobacco and alcohol abuse. These factors should be re-discussed with the patient in each subsequent phase of treatment for GERD.

23. Phase II (4-8 week trial) Full Dose H_2RA Therapy

Full-dose therapy (cimetidine 400 mg bid, ranitidine 150 mg bid, famotidine 20 mg bid, and nizatidine 150 mg bid) for four to eight weeks as a trial is recommended. A PPI is not recommended on an empiric basis due to cost issues and long-term maintenance requirements.

25. Encourage Step-Down Therapy

Patients with uncomplicated reflux may benefit from step-down therapy. Step-down therapy gradually reduces the intensity of treatment as tolerated to maintain the patient in remission. Lifestyle modifications should be continued indefinitely. In a follow-up study of six years duration, patients whose initial symptoms were controlled by lifestyle measures initially required only these and occasional H_2RAs 80% of the time. Patients initially requiring H_2RAs were controlled with lifestyle measures and intermittent H_2RAs 67% of the time.

27. Continue Therapy

Most patients with typical reflux symptoms will respond to acid suppressive therapy. This guideline encourages trying to reduce the therapy over time but many patients will stay on such therapy for months if not years. As long as these patients are not symptomatic, they do not require an endoscopy.

Some groups have suggested, however, that patients with reflux should have an endoscopy to screen for Barrett's esophagus (BE). BE is a change in the lining of the esophagus from the normal squamous mucosa to a metaplastic intestinal columnar mucosa. Patients with BE are at increased risk of adenocarcinoma of the esophagus and thus patients with BE are placed into endoscopic surveillance programs.

The American College of Gastroenterology recommends: "Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo endoscopy."

At present there are no data to demonstrate the cost effectiveness of such a strategy. Patients with longer duration of symptoms (>10 years) are more likely to have BE. White men are at increased risk. Selecting patients on the basis of risk would improve the cost effectiveness but has not been incorporated into guidelines. Given the absence of clear evidence of benefit, screening for Barrett's esophagus in patients with GERD cannot be advocated in all patients.

28. Endoscopy

Flexible esophagogastroduodenoscopy should be used for the initial evaluation of esophageal symptoms in patients suspected of having GERD with refractory heartburn, odynophagia, or extra esophageal symptoms. Endoscopy permits direct inspection and biopsy of the esophageal lining, aiding detection of grade 1 or grade 2 esophagitis--changes not apparent on x-rays. Endoscopy also permits detection and biopsy of Barrett's esophagus.

29. Positive (Moderate Esophagitis)?

Patients with erosions, ulcerations, strictures or intestinal metaplasia (Barrett's esophagus) are considered to have a positive endoscopy. Patients who have either a normal esophageal examination or only distal esophageal erythema (mild esophagitis) are considered to have a negative endoscopy.

30. Case Management

Patients with erosive esophagitis or worse should be treated with proton pump inhibitors in a standard therapeutic dose. Patients intolerant of PPIs may receive a quadruple therapeutic dose of H_2RA. Failure to respond should prompt doubling the dose of the antisecretory medication and referral to gastroenterology. Duration of treatment should be 8 weeks.

Relapse within 6 months of discontinuing treatment is the rule rather than the exception. For that reason, combined with the lack of studies supporting step-down therapy for moderate or worse esophagitis, maintenance treatment with the medication providing healing is recommended.

Patients requiring long-term maintenance therapy or those who are incompletely controlled on maintenance therapy may wish a surgical opinion regarding fundoplication.

Cisapride has been removed from the guideline; it is no longer available.

See listing of proton pump inhibitors above.

31. Phase III (Negative Endoscopy)

Diagnosing GERD can be difficult in patients with atypical symptoms, non-cardiac chest pain, or normal endoscopy. Many diagnostic tests to find pathological reflux have been developed. Few of them have withstood rigorous scientific testing and lack relevance to clinical management. 24-hour pH monitoring has been adopted as the diagnostic test of choice in patients with symptoms of unknown cause. In addition, one published trial and practical experience suggest short-term administration of high-dose proton pump inhibitors (PPIs) can reduce symptoms and offer a reasonably accurate diagnostic discrimination in selected groups of patients with suspected GERD. All patients with complaints of heartburn do not necessarily all have GERD. Patients who don't respond to therapy, and have negative pH studies should be considered to have functional heartburn. These patients should be individually managed, as are patients with other functional gastrointestinal disorders (i.e. irritable bowel syndrome, non-ulcer dyspepsia.)

Definitions:

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

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A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study

- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

Detailed and annotated clinical algorithms are provided for:

- Dyspepsia
- Gastroesophageal Reflux Disease (GERD)

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

General Benefits

- Appropriate evaluation of epigastric discomfort and management of gastroesophageal reflux disease (GERD).
- Appropriate diagnosis of underlying disease in patients with upper gastrointestinal tract pain or discomfort, such as duodenal ulcer, gastric ulcer, non-ulcer dyspepsia, or GERD.
- Timely management and treatment of patients with dyspepsia, including relief of symptoms

Specific Benefits

Helicobacter pylori testing and treatment for Helicobacter pylori infection

- Helicobacter pylori testing appears to be a cost-effective approach for long-term dyspepsia management.
- A decision-analytic model shows that an approach utilizing a combination of empiric therapy for Helicobacter pylori and antisecretory therapy was superior to antisecretory therapy alone. In addition, initial therapy for Helicobacter pylori guided by serological testing was the most cost-effective option if the cost of the serologic test was $12 or less. When endoscopy can be provided for less than $500 including all fees, immediate endoscopy is more cost-effective.
- A second decision analysis comparing the costs and outcomes of initial anti-Helicobacter pylori treatment to initial endoscopy among those who are Helicobacter pylori antibody positive shows initial therapy as the most cost effective management strategy.

Discontinuation of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Continued NSAID use decreases the rate of healing of gastric and duodenal ulcers with either histamine-2 receptor antagonists (H_2RAs) or proton pump inhibitors (PPIs). Cessation of NSAID use during ulcer treatment results in healing rates comparable to those in patients who have not had NSAIDs. For gastric ulcers, a healing rate of 71% was noted after 4 weeks in those receiving an H_2RA, compared to 54% in those continuing on an NSAID during their H_2RA treatment. At 8 weeks, the comparable values were 95% and 63%. Finally, at 12 weeks of treatment, the two groups showed healing rates of 100% vs. 79%.
- For duodenal ulcers, the rate of healing at 4 weeks was 74% on H_2RAs for those stopping NSAIDs compared to 57% for those continuing to use NSAIDs. The comparable rates after 8 weeks were 100% and 92%. Thus, for a patient not able to discontinue NSAIDs during treatment, a course of treatment of 8 weeks with proton pump inhibitors is recommended.

Gastroesophageal Reflux (GERD)

- A recent study comparing the onset of action, potency and duration of effect of an over-the-counter H_2RA with an over-the-counter calcium carbonate preparation shows that either of these agents reduces gastric acid and reduces heartburn more effectively than does a placebo. The oral antacid had a more rapid onset of action within 30 minutes but a duration of effect of only 60 minutes. By comparison, famotidine in this trial had an onset of action beginning after 90 minutes but a duration of effect of greater than 540

minutes. The peak potencies of the two agents in recommended doses were similar.

- The four available H_2RA (cimetidine [Tagamet® and generics], ranitidine [Zantac® and generics], famotidine [Pepcid®], and nizatidine [Axid®]) appear to be equivalent in efficacy in the management of GERD when given in equipotent acid-suppressive doses. The adverse event profiles of these agents appear to be similar as well.
- In a follow-up study of six years' duration, 80% of patients whose initial symptoms were controlled by lifestyle modifications alone required ongoing lifestyle measures and only occasional H_2RAs for symptom relief. Of patients initially requiring H_2RAs, 67% were controlled with lifestyle measures and intermittent H_2RAs.
- 24-hour pH monitoring has been adopted as the diagnostic standard for GERD. 24-hour pH monitoring measures longer periods, captures transient pH changes not associated with symptoms, and can be coded into a scientific scoring system yielding acceptable sensitivities. These strengths make it the most useful test in patients with surreptitious disease and normal endoscopy. However, pH monitoring does not provide evidence of causality.
- Proton pump inhibitors (PPIs) are capable of marked acid suppression and may allow a simultaneous empiric, therapeutic, and diagnostic trial. In the only study to be fully published, Schindlbeck, et al demonstrated an 83.3% sensitivity of omeprazole (40 mg bid for seven days) in reducing symptoms in 75% of patients with GERD symptoms, normal endoscopy, and abnormal pH monitoring studies. Omeprazole in a dose of 20 mg bid was not effective.

POTENTIAL HARMS

The adverse event profiles of histamine-2 receptor antagonists (H_2RAs) appear to be similar. However, cimetidine generally exhibits a greater potential for drug-drug interactions at the level of hepatic drug metabolism than the other three agents (ranitidine, famotidine, nizatidine). The significant interaction potential with theophylline, warfarin, and phenytoin may prompt the clinician to either not use cimetidine or to use cimetidine cautiously, following serum drug concentrations (theophylline, phenytoin) or indicators of pharmacodynamic effect (international normalization ratio [INR] for warfarin) where available. The clinician also needs to be cognizant of interactions with drugs which require an acid environment for absorption (e.g., tetracycline, ketoconazole). In this case, all histamine-2 receptor antagonists will react.

QUALIFYING STATEMENTS

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- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for release, a member group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment and tobacco cessation.

The following detailed measurement strategies are presented to help close the gap between clinical practice and the guideline recommendations.

Priority Aims and Suggested Measures for Health Care Systems

1. To increase the use of recommended methods for evaluating dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients evaluated for dyspepsia with testing for Helicobacter pylori (H. pylori).
   b. Percentage of patients evaluated for dyspepsia without standard single-phase contrast studies.
   c. Percent of patients evaluated for dyspepsia with endoscopy prior to receiving a therapeutic trial who do not have an alarm feature present.
2. To increase appropriate pharmaceutical treatment of patients with dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with dyspepsia with positive H. pylori who receive antibiotic therapy.
   b. Percentage of patients with dyspepsia treated with antibiotics for positive H. pylori who receive effective therapy.
   c. Percentage of patients with dyspepsia treated with a proton pump inhibitor (PPI) or long-term histamine-2 receptor agonist (H_2RA) without previous endoscopic examination.
3. To decrease complications associated with peptic ulcer disease.

   Possible measure of accomplishing this aim:

   a. Number (or rate) of hospital admissions for ulcer hemorrhage.

4. To improve (functional) outcomes and satisfaction of patients with dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients evaluated with dyspepsia with improved symptoms following treatment as measured by a dyspepsia-specific health status instrument.
   b. Percentage of patients with dyspepsia who report that they are satisfied or very satisfied following treatment for dyspepsia.

Note: There are no specifications written for the possible measures listed above. The Institute for Clinical Systems Improvement (ICSI) will seek input from medical groups on what measures are of most use as they implement the guideline. In a future revision of the guideline, one or two measurement specifications may be included.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute For Clinical Systems Improvement (ICSI). Dyspepsia. Bloomington (MN): Institute For Clinical Systems Improvement (ICSI); 2003 Jan. 48 p.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Oct (revised 2003 Jan)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, CentraCare, Community-University Health Care Center, Dakota Clinic, ENT SpecialtyCare, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, RiverWay Clinics, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians

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GUIDELINE COMMITTEE

Committee on Evidence-Based Practice

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. It is not assumed that these

financial interests will have an adverse impact on guideline content. They simply are noted here to fully inform users of the guideline.

All work group members: none declared.

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the revised guideline: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from the Institute for Clinical Systems Improvement, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; email: icsi.info@icsi.org; Web site: www.icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Dyspepsia. In: ICSI pocket guidelines. April 2002 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2002 Mar. pp. 308-314.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; e-mail: icsi.info@icsi.org; Web site: www.icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

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